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Deformation imaging and three-dimensional echocardiography : implications on clinical management of patients with ischemic heart disease

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CHAPTER 1

General introduction and outline of the thesis



GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Cardiovascular disease remains one of the leading causes of death in the Western world.¹ It accounts for 1 of every 3 deaths in the United States of America, of which approximately 40% caused by coronary heart disease.^{1,2} According to the World Health organization, the number of deaths due to cardiovascular disease will increase to 23.3 million by 2030.¹ Moreover, from 2000 until 2010, a 28% increase was found in the number of inpatient cardiovascular operations and procedures in the United States of America.²

Acute myocardial infarction is a major cause of death. The percentages of acute coronary syndromes with ST-segment elevation myocardial infarction (STEMI) varies between 29% and 47%.^{3,4} The use of evidence-based therapy and primary percutaneous coronary intervention (PCI) has led to improvements in short-term survival and reduction in left ventricular (LV) infarct size, thereby improving LV function and preventing LV remodeling.⁵ However, these improved short-term outcomes have resulted in a growing and aging population that is at increased risk for developing heart failure and experiencing re-infarction and sudden cardiac death during long-term follow-up, resulting in a significant socioeconomic burden.^{6,7} The current guidelines regarding management of STEMI and heart failure patients therefore focus on optimization of care, secondary prevention and risk stratification of this population.⁸⁻¹⁰ Multimodality imaging, especially echocardiography, has played a fundamental role in the risk stratification of patients with ischemic heart disease, in particular after STEMI.

Echocardiography for the risk stratification of patients with ischemic heart disease

In daily clinical practice, echocardiography has been frequently applied in the management of patients with ischemic heart disease.⁸⁻¹¹ This safe, inexpensive and widely available imaging modality can be easily used at the bedside and is the imaging technique of first choice for surveillance.¹¹ Generally, echocardiography is useful to establish the diagnosis, location and extent of a myocardial infarction and to detect complications after myocardial infarction.¹¹ More importantly, the prognosis and risk stratification in the acute phase and during follow-up of ischemic heart disease patients can be assessed using echocardiography. In Table 1, an overview is provided of prognostic echocardiographic parameters in ischemic heart disease.

LV systolic function is an important prognostic determinant in ischemic heart disease and should be assessed according to current STEMI, heart failure and echocardiographic guidelines.^{8-10,12-14} Acutely after myocardial infarction, extensive myocardial damage occurs resulting in reduced contractile reserve, which could persist or even deteriorate if ongoing ischemia exists. At follow-up, LV dilatation due to infarct expansion and stretching of the myocardial scar could result in reduced LV systolic function.

Table 1. *Echocardiographic parameters associated with prognosis in ischemic heart disease*

CONVENTIONAL ECHOCARDIOGRAPHY	
• Left ventricular function	• Wall motion score index
	• Left ventricular ejection fraction
	• Left ventricular excursion
• Left ventricular volumes	
• Mitral regurgitation	
• Left atrial volume	
• Diastolic function	
• Right ventricular function	
• Right ventricular dimensions	
• Systolic pulmonary arterial pressure	
ADVANCED ECHOCARDIOGRAPHY	
• Left ventricular function	• Wall motion score index
	• Left ventricular ejection fraction
	• Longitudinal strain (global and regional)
	• Left ventricular excursion
• Left ventricular volumes	

Traditionally, LV ejection fraction (LVEF), a volume-based measure, has been used to measure LV systolic function. Management decision making in ischemic heart disease strongly relies on LVEF, in particular the usage of device therapy such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs).^{8-10,12,15,16} However, LVEF is a relatively insensitive, observer dependent measurement. Furthermore, LVEF has proven to be a relatively insensitive tool of LV performance and has limited accuracy to identify patients at risk for ventricular arrhythmias.¹⁷⁻²⁰ In the last years, several advances in echocardiography resulted in evaluation of novel indices in order to improve characterization of LV function and thereby stratification of patients with ischemic heart disease. Speckle-tracking strain echocardiography provides more insight in cardiac mechanics and LV performance.²¹⁻²⁴ A more sensitive assessment of both regional and global myocardial contraction can be performed using this technique.^{25,26} Figure 1 provides an example of this echocardiographic method. In ischemic heart disease patients, speckle-tracking strain echocardiography has been associated with the occurrence of all-cause mortality, re-infarction and ventricular arrhythmias, indicating its value in daily clinical practice.²⁷⁻³⁰

LV volumes also add significant prognostic information to the risk stratification of patients with ischemic heart disease.³¹ LV adverse remodeling post-infarction, observed in

approximately 30% of acute myocardial infarction patients, has been associated with an increased risk of mortality and development of heart failure.³²⁻³⁶

Another prognostic echocardiographic measure is the presence and severity of MR.³⁷ Acutely after myocardial infarction, ischemic MR is frequently observed.³⁸⁻⁴⁰ On the other hand, functional ischemic MR is a highly dynamic lesion that is likely to improve after coronary revascularization or to impair as a result of progressive LV adverse remodeling and tethering of the mitral leaflets.^{41,42} Furthermore, it has been associated with long-term mortality and the development of heart failure.^{38,43} Yet, data on the time course and prognostic implications of functional ischemic MR in the contemporary era of primary PCI has not been explored to date.

Last but not least, right ventricular (RV) function and dimensions are also important prognostic markers in ischemic heart disease. Especially, RV dysfunction portends a poor prognosis post-myocardial infarction.⁴⁴⁻⁴⁶ However, RV function may recover within days or weeks, particularly after successful reperfusion.^{47,48} Not surprisingly, the current guidelines recommend evaluation of RV function in ischemic heart disease.^{8-10,13,14} Notably, while LV remodeling received much attention in ischemic heart disease, less research is conducted on RV remodeling using echocardiography in the primary PCI era, underscoring the need of additional studies regarding this phenomenon.⁴⁹⁻⁵¹

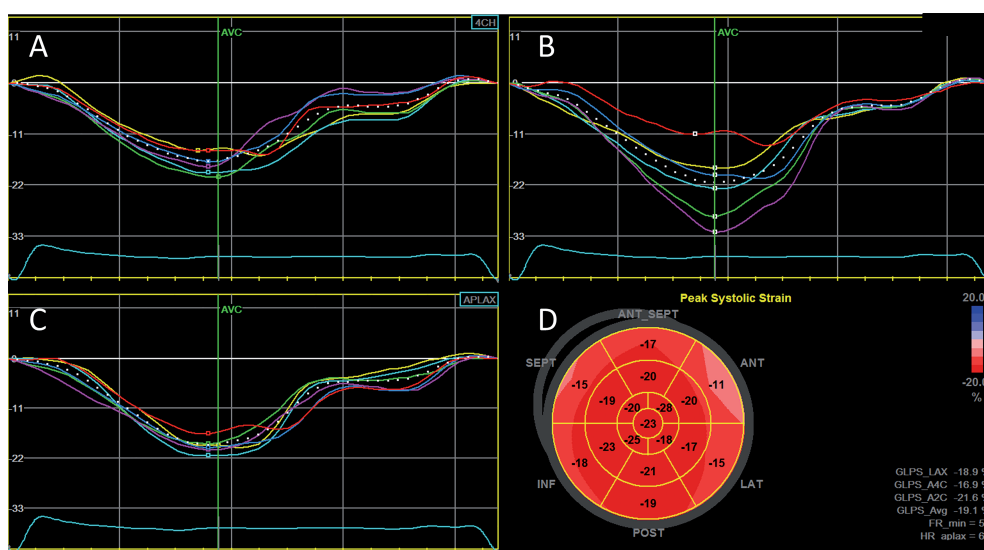


Figure 1. Example of global longitudinal peak systolic (GLPS) strain curves from the 3 apical views of the left ventricle (panel A, 4-chamber view [4CH]; panel B, 2-chamber view [2CH]; panel C, parasternal short-axis view [APLAX]) and summarizing 17-segment bull's eye plot (panel D). The software (EchoPac, GE Medical Systems, Horten, Norway) provides longitudinal peak systolic strain for every segment and for every apical view separately (GLPS_A4C, GLPS_A2C and GLPS_LAX, respectively) and calculates a global longitudinal peak systolic strain value for the entire left ventricle (GLPS_Avg). ANT = anterior wall; ANT_SEPT = antero-septal wall; AVC = aortic valve closure; HR = heart rate; INF = inferior wall; LAT = lateral wall; POST = posterior wall; SEPT = septal wall.

Stress echocardiography for detection of myocardial ischemia and viability

Following an acute myocardial infarction, the presence of residual and/or ischemia provides additional prognostic information.⁵²⁻⁵⁷ Stress echocardiography is one of the recommended tools to detect and localize (residual) ischemia post-myocardial infarction, of which dobutamine stress echocardiography (DSE) is the most widely used method.^{10,56,58,59} Conventionally, regional wall motion and thickening is visually assessed resulting in a wall motion score. However, this semi-quantitative method is challenging, since it is highly subjective and image quality dependent, even when performed by expert observers.^{60,61} Therefore, more quantitative and objective approaches, such as speckle-tracking strain echocardiography and 3-dimensional echocardiography, could overcome these practical limitations of DSE. These approaches do not depend on geometric assumptions or on experience and can be performed semi-automatically. Moreover, global and regional assessments of the myocardium are possible. Hence, these quantitative tools could be useful to accurately detect ischemia. As for speckle-tracking strain echocardiography, this method has been validated against sonomicrometry and evaluated in coronary artery disease patients.⁶²⁻⁶⁸ However, its value in STEMI patients, in whom DSE is particularly challenging due to the presence of existing wall motion abnormalities, has not been investigated to date. Three-dimensional echocardiography has the advantages of overcoming the limitations of 2-dimensional echocardiography, including no geometric assumptions, optimization of image position with no or little foreshortened views, better possibilities of endocardial boundary tracing and a good reproducibility.⁶⁹⁻⁷² An example of 3-dimensional LV volume analysis is shown in Figure 2. Three-dimensional echocardiography could be valuable in the assessment of DSE. An abnormal LV volume response during dobutamine infusion (LV dilatation) has been proposed as marker of ischemia.⁷³⁻⁷⁵ In patients with suspected coronary artery disease, this parameter was associated with more severe coronary artery disease and an increased risk of adverse events, including death and myocardial infarction.⁷³⁻⁷⁵ Another possible application of 3-dimensional echocardiography during DSE could be the assessment of LV excursion. This measure reflects the longitudinal contraction of the LV, which is initially affected in ischemia.⁷⁶⁻⁷⁹ Since previous studies demonstrated a correlation between LV excursion assessed during 2-dimensional stress echocardiography and the presence of coronary artery disease, this could be a promising tool in 3-dimensional DSE.^{76,80-82}

Treatment options in ischemic heart failure: echocardiographic evaluation

Ischemic heart failure is a complex syndrome with many treatment options aiming to improve survival and to prevent progression of symptoms. Pharmaceutical treatment and lifestyle interventions, on the one hand, are the 2 cornerstones of heart failure treatment.⁸ On the other hand, heart failure guidelines have certain recommendations regarding treatment modalities like surgical treatment (e.g. revascularization via PCI or coronary artery bypass surgery, valvular surgery, surgical ventricular restoration), device implantation (e.g.

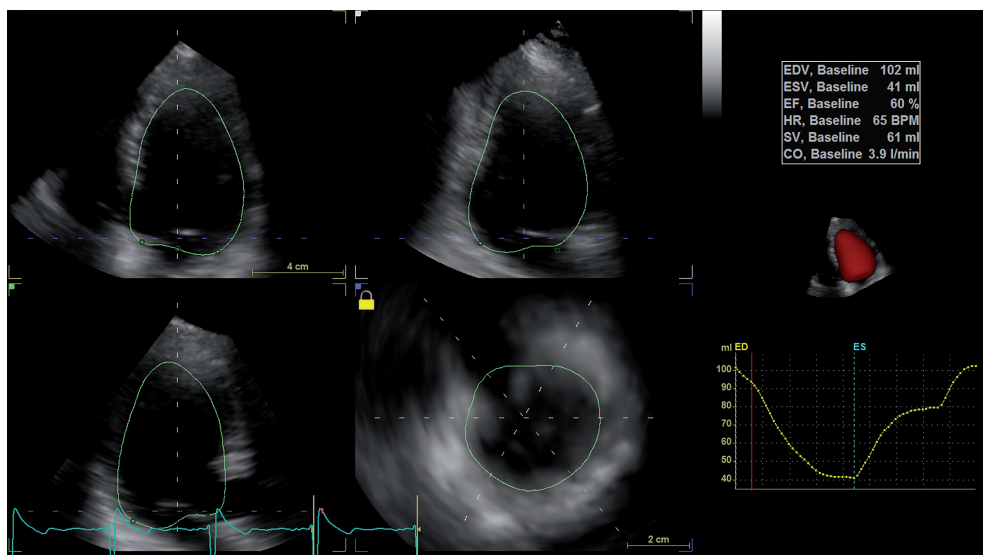


Figure 2. Example of 3-dimensional left ventricular volume analysis obtained by post-processing of a full-volume 3-dimensional dataset. In the left panel, the 3-dimensional dataset is automatically displayed (according to the software EchoPac, GE Medical Systems, Horten, Norway) to visualize the 4-chamber (top left), the 2-chamber (top right) and the parasternal short-axis views (bottom left). After manually indicating the mitral annulus by 4 points and left ventricular apex on the end-systolic and end-diastolic frames, the software automatically identifies the entire endocardial border in each frame. If required, manual adjustment of the endocardial contour is possible. From this, the 3D cast of the left ventricle is created (central right panel). Subsequently, left ventricular volumes and ejection fraction are automatically quantified (top right panel). In the lower right panel, left ventricular volume is plotted over time throughout the cardiac cycle. CO = cardiac output; ED = end-diastole; EDV = end-diastolic volume; EF = ejection fraction; ES = end-systole; ESV = end-systolic volume; HR = heart rate; SV = stroke volume.

ICD, CRT) and mechanical cardiac support (e.g. (left) ventricular assist device).^{8,12,15,16,83}

Therefore, it is of utmost importance to evaluate which treatment options are most suitable in heart failure patients. To warrant the appropriate therapy strategy, cardiac imaging, especially echocardiography, plays a key role.⁸ As recommended by the European Society of Cardiology, the echocardiographic evaluation should at least include assessment of cardiac anatomy (e.g. volumes, dimensions, mass) and function (e.g. LV function and wall motion, RV function, valvular function, pulmonary artery pressure).⁸

Patients with ischemic heart failure can present with various manifestations on echocardiography guiding treatment decision making. LV adverse remodeling, an important prognostic factor, has several treatment options. Surgical ventricular restoration, in combination with coronary artery bypass surgery, could be considered in patients with increased LV end-systolic volumes in order to exclude scar tissue from the LV wall.⁸³ Another therapeutic option could be CRT implantation, an effective therapy in selected patients, including LVEF $\leq 35\%$ and a broad QRS duration, resulting in improvements in symptoms and long-term mortality.^{16,84-86} More importantly, CRT has demonstrated to slow or even reverse LV adverse remodeling.^{85,87} However, 20% to 40% of patients do not respond to

CRT according to current definitions to CRT response.⁸⁷⁻⁹⁰ Studying the different definitions of response to CRT could enable cardiologists to select the group of patients who truly respond to CRT.

Due to LV dilatation, functional MR could be observed as a result of reduced leaflet coaptation. Depending on the symptomatology, patients' comorbidity, LV systolic function, LV dimensions (e.g. LV end-diastolic diameter) and the presence or absence of significant coronary artery disease, ischemic MR could be treated by mitral valve repair (in combination with coronary artery bypass surgery), mitral valve replacement or percutaneous edge-to-edge repair (MitraClip).⁸ However, patient selection has proved to be suboptimal: the advantageous LV reverse remodeling following surgical mitral valve repair has only been reported in 40% to 52% of heart failure patients with moderate to severe functional MR.⁹¹⁻⁹³ Consequently, research to improve identification of patients who will benefit from one of these treatment modalities is warranted.

Additionally, the risk of sudden cardiac death should be evaluated. LVEF is a major determinant of ventricular arrhythmias and an established criterion to select patients for ICD implantation.^{12,15,94} As highlighted above, LVEF has proved to have limited specificity to identify patients who will benefit from ICD.^{17,19} Therefore, more insights in the arrhythmogenic substrate of ventricular arrhythmias, including substrate characterization, could aid in implanting ICD in the appropriate patients to prevent sudden cardiac death.

Finally, if conventional treatment options are not eligible and patients are diagnosed with end-stage heart failure, advanced and experimental treatment options could be considered including heart transplantation, mechanical cardiac support (either as bridge to transplantation or as destination therapy) and cell therapy.⁸

Outline of the thesis

The objective of this thesis was to evaluate the role of echocardiography for the risk stratification and treatment guidance of patients with ischemic heart disease.

In **Part I**, the value of echocardiography was investigated in ischemic heart disease, in particular in the acute setting post-STEMI and during follow-up until 12 months after the index infarction. The time course of several parameters as well as the application of advanced echocardiography was addressed. **Chapter 2** analyses the border zone, assessed by speckle-tracking strain echocardiography, as a potential risk factor for ventricular arrhythmias. **Chapter 3** evaluates the changes in RV dimensions and function, including RV remodeling. **Chapter 4** discusses the time course of MR following STEMI in relation to adverse outcome. **Chapter 5** provides more insight in the subtle changes in LV systolic function in a cohort of STEMI patients with diabetes. **Chapter 6** describes a novel technique, LV excursion, to quantify 3-dimensional DSE in relation to the presence of coronary artery disease in patients with suspected coronary artery disease.

Part II focuses on the role of echocardiography in decision making in patients with chronic ischemic heart disease who developed heart failure, especially in CRT, cardiac surgery and ICD therapy. **Chapter 7** investigates the role of the biomarker N-terminal pro-brain natriuretic peptide as marker of CRT response. Finally, **Chapter 8** provides more insight in the temporal heterogeneity of segmental myocardial deformation in order to improve risk stratification of ventricular arrhythmias in patients with ischemic heart disease.

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